This Month in Genetics

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When Being the Same Makes You Different

Twenty years ago, homozygosity mapping was developed as an alternative to linkage analysis for the identification of candidate regions for autosomal-recessive disorders. These methods were originally used in inbred families to identify regions of homozygosity by descent. Large regions of homozygosity would not be expected in outbred populations, and thus, regions of extended haplotype homozygosity have been used to identify genomic regions that might have undergone natural selection. In a recent issue of *PNAS*, Lencz et al. took these ideas and applied them to complex genetic traits in outbred populations. They developed a method of whole genome homozygosity association (WGHA) and identified, in an outbred white American population, 339 common homozygosity runs that included at least 100 consecutive SNPs. Reasoning that signatures of selection are strong around genes involved in neurodevelopment, they identified nine homozygosity runs that were more common in a sample of individuals with schizophrenia than in a group of controls, including one region that was exclusive to the case population. Four of these regions contained, or neighbored, genes that have been previously implicated in schizophrenia. Although rare, these runs of homozygosity might explain a proportion of schizophrenia through a high penetrance, recessive effect.

T. Lencz et al. (2007). Proc. Natl. Acad. Sci. USA. 104, 19942–19947.

Sing, Sing a Song

The complexities of human speech and language are something that sets us apart from other animals, so the report by Lai et al. in 2001 (*Nature* 413, 519–523) that a single-gene mutation was responsible for a severe speech and language disorder was met with great excitement. The mutated gene, *FOXP2*, has since been studied with interest as a potential gene that might have played a big role in what makes us human. Songbirds are another type of animal that has fairly complex communication, and just as we learn to speak by imitating our parents, songbirds learn to speak by imitating a tutor. During the period when young zebra finches are learning to sing, expression of *Foxp2*, which is a highly conserved gene, is transiently increased in the area of the brain important for song development. These factors lead Haesler et al. to study the role of *Foxp2* in zebra finch vocal learning by using a knockdown RNAi strategy to reduce FoxP2 levels in this part of the brain prior to vocal learning. Birds with reduced expression of FoxP2 imitated their tutor's song with less precision and sang more variably than control birds, and this was not due to an inability to generate particular sounds. Instead, the authors propose that the defect lies in the ability of the birds to match their vocal output to that of their tutor. It has been proposed that people with *FOXP2* mutations have deficits in the complex orofacial movements required for speech. The data in birds suggest that the true underlying defect might instead be one of motor learning.

S. Haesler et al. (2007). PLOS Biology 5, e321. 10.1371/journal.pbio.0050321.

The Ins and Outs of Nonallelic Homologous Recombination

Nonallelic homologous recombination (NAHR) between highly similar duplicated sequences gives rise to genomic disorders, which are caused by altered copy number of dosage-sensitive genes. We often think of these events as causing deletions, but the reciprocal duplications are also possible. For some loci, both the deletion and the reciprocal duplication are associated with genomic disorders, one example being hereditary neuropathy with liability to pressure palsies (HNPP) and Charcot-Marie-Tooth type 1A (CMT1A). With the prevalence of genomic disorders in the population, attempts have been made to estimate the rates at which the duplication and deletion events occur, but these estimates can be biased if the deletion and duplication events are not diagnosed with equal efficiency or if one or the other event causes embryonic lethality. To avoid these biases, Turner et al. developed a sperm-based assay to directly measure the duplication and deletion events at four NAHR hot spots in five sperm donors. At each of the four sites, deletions occurred at a higher rate than the reciprocal duplications, thus refuting the idea that the reciprocal events occur with equal frequency. In addition to suggesting that intrachromatidal NAHR is the predominant mechanism of NAHR at these sites, the relative ratio of deletions to duplication events suggests that the prevalence of genomic disorders as diagnosed in the

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population is not reflective of the underlying rates of these events and that some of these disorders might be greatly underdiagnosed.

D.J. Turner et al. (2007). Nat. Genet. Published online December 2, 2007. 10.1038/ng.2007.40.

Progress on Stem Cell Therapy for Sickle Cell Disease

Proponents of embryonic stem cells have argued that they might be used to cure everything from Parkinson disease to spinal-cord damage. Clearly, these approaches have not been without detractors, and that is why there has been such excitement over recent studies that have reported the generation of embryonic stem cell-like cells from fibroblasts, a process that obviates the need for embryos. These induced pluripotent stem cells (iPS) are generated through retroviral transduction of a combination of transcription factors and are highly similar to embryonic stem cells on the basis of several criteria. Hanna et al. now show that iPS can be used to treat genetic disease in a mouse model of sickle cell anemia. These mice, which express the human α and β globin genes in place of the corresponding mouse genes, are homozygous for a sickling mutation in β globin. Fibroblasts from the sickle cell mice were used to generate iPS cells, and the genetic defect in these cells was corrected via homologus recombination to replace the β^S allele with a wild-type β globin allele. The corrected iPS cells were transplanted back into the sickle cell mice, who had since been irradiated. For at least 12 weeks after transplantation, this treatment increased red blood cell counts and hemoglobin levels, normalized the mean corpuscular volume, and improved the red cell morphology. Although there are several safety hurdles to overcome before this type of approach could be attempted in humans, the promise of stem cells for treatment of human disease seems one large step closer.

J. Hanna et al. (2007). Science. Published online December 6, 2007. 10.1126/science.1152092.

Rules of Recombination

Chromosomes obviously have some rules for the placement of recombination events—such as a dearth of crossovers near centromeres and an increase in relative crossover rates on smaller chromosomes—we just don't have a full rulebook yet. To study recombination control mechanisms, Blitzblau et al. studied the placement of recombination in *Saccharomyces cerevisiae* by mapping the ssDNA intermediates that surround the sites of chromosome double-strand breakage (DSB). Rather than the reduced number of DSBs expected near centromeres, a substantial number of DSB hotspots were found in the pericentromeric regions, suggesting that recombinational suppression at centromeres does not prevent the DSB itself but rather occurs at the level of DNA repair. In contrast, the reduced frequency of DSBs near telomeres was predicted by crossover suppression at telomeres, but it was observed in a much smaller window than has been measured previously. Unexpectedly, this DSB-poor region neighbored a region that was 20–120 kb from the telomere and that exhibited a marked increase in DSB events across all chromosomes. This telomere-proximal enrichment of DSBs increases the relative density of DSBs on small chromosomes and might be a way by which the smaller chromosomes are ensured to have a crossover event, which is necessary for proper chromosome segregation at meiosis. Although maybe our recombination rulebook still isn't complete, we now have additional general principles to help us understand the rules.

H.G. Blitzblau et al. (2007). Curr. Biol. 17, 2003–2012.